Remarks/Argument

Applicant and Applicant's representative appreciate the opportunity on July 18, 2005 to meet with Examiners Ashen and Wang to discuss the claimed invention. Their input and suggestions were very helpful, and as suggested in the Interview Summary presented by the Office at the time of the Interview, Applicant has attached hereto a detailed Declaration of Dr. Alan M. Gewirtz. Applicant has also amended the claims to more clearly distinguish the dsRNA used to initiate disruption of target gene expression in vitro in a human cell, from hairpin or other types of dsRNA. In the present invention the two linear complementary strands are independently controlled to produce the paired RNAs, as supported for example in Applicant's specification at paragraphs 0035, 0036 and 0052.

Claims 1, 2, 5, 7-9, 11, 14, and 17-22 were pending in the application at the time of the outstanding Office Action. The claims have been amended, claims 14 and 17-20 are hereby cancelled, and new claims 23-27 are hereby added to further the prosecution of this case to allowance, without any admission that any claim being cancelled by the present Amendment is not patentable. Applicant reserves the right to later prosecute any cancelled claim in a Divisional or CIP application. No new matter has been added, and support for the claims to the *in vitro* subject matter has been clearly recognized by the Examiner in previous communications.

Based on the above changes and the following remarks, Applicant respectfully requests reconsideration of the claims and withdrawal of the pending rejections.

Response to §112 (1st) Rejections re *in vitro* Methods

Claims 1, 2, 5, 7-9, 11, 14 and 17-22 remain rejected under 35 U.S.C. §112, 1st paragraph as allegedly failing to comply with the written description requirement. However, in light of Applicant's arguments of record made in Responses to previous Office Actions regarding the written description requirement and the level of support needed to respond to an inquiry into the level of provided written description, particularly since the courts have supported a strong presumption that an adequate written description of the claimed invention is present in the specification as filed, Applicant respectfully submits that one skilled in the art, upon reading the specification as filed, would have

understood what was meant by an RNA that is homologous to the target gene. Thus, it is shown that the Applicant was in possession of the claimed invention.

As previously noted, the Examiner asserts that the specification lacks specific guidance concerning what level of nucleotide sequence homology is required of an RNA for use in the instant invention and what the structure is of an RNA that would correspond with the function of targeting any gene. However, the degree of homology for the claimed invention is inherently disclosed in the examples in the specification and this would be recognized by one skilled in the art. Specifically, the examples in the specification teach making RNA strands for annealing to make the dsRNA molecule using *in vitro* transcription reactions.

The *in vitro* transcription reactions use a DNA template which provides the sequence to which a homologous RNA strand is desired. RNA polymerases, specifically SP6 RNA polymerase and T7 RNA polymerase are well-known polymerases, which have known error rates. Given these known error rates and the number of nucleotides in the transcripts made, one skilled in the art can calculate the number of errors expected in each RNA strand (see such calculation for the two different sized transcripts used in the examples). Assuming that each RNA strand will have independent errors (*i.e.*, errors will not always be at the same positions), one can add together the two numbers of errors expected to get the number of errors expected in a dsRNA. This sum, therefore, allows one to calculate the degree of homology of the dsRNA to its target gene (transcript length minus the total number of errors divided by the transcript length x 100%).

Furthermore, the specification provides teachings on the length of the dsRNA homologous to a target gene. In the examples, a representative long dsRNA molecule of 828 bp (see page 12, lines 28-31) homologous to cKitR was employed in the method to induce RNAi. This number, therefore, provides an upper limit on what sized dsRNA is successfully used in the method claimed. A lower limit on the size of the dsRNA is evident in the logic used in designing antisense molecules. See, for instance, page 47 under "Theoretical limits of specificity" in Branch (1998).

Given the size of the human genome, any sequence that is 17 nucleotides or longer has a high probability of being unique. Since the mechanism of RNAi is homology to a particular sequence, one skilled in the art knows that the minimum dsRNA

size to achieve target specificity is 17 nucleotides. Therefore, the range of size for dsRNA appropriate for use in the instant invention is 17 to about 830 basepairs.

The specification discloses four general methods of obtaining dsRNA for use in the instant invention. See page 1, line 30 through page 2, line 28. The preferred method is set forth in the example. See page 12, line 28 through page 13, line 12. Specifically, the two strands of RNA are made in an *in vitro* transcription reaction using a DNA template comprising a fragment of the target gene subcloned into an expression vector having an SP6 promoter and a T7 promoter. *In vitro* transcription reactions using the cognate RNA polymerases followed by strand annealing and purification yields the dsRNA molecule homologous to the target gene.

Accordingly, Applicant's specification teaches the degree of homology for the dsRNA used in the claimed invention, as well as the range of sizes for the dsRNA (from 17 to about 830 bp) and the method of making dsRNA homologous to the target gene. Based upon the disclosure in the specification as filed and the knowledge imputed to the skilled artisan at the time, a skilled artisan would indeed understand that Applicant had possession of the claimed subject matter. Moreover, with regard to Applicant's method for disrupting target gene expression *in vitro* at the mRNA level in a human cell, the record shows that the Examiner has stated that the specification enables the use of RNAi *in vitro* to practice methods of disrupting KitR gene expression in human cancer cell lines using Kit dsRNA (KdsRNA). Therefore, Applicant respectfully requests reconsideration and withdrawal of the 35 U.S.C. § 112, first paragraph, written description rejection.

Response to §112 (1st) Rejections re *in vivo* Methods

Claims 1, 5, 7, 9, 11, 14 and 17-22 have been rejected under 35 U.S.C. 112, 1st paragraph as lacking enablement for using RNAi to disrupt gene expression *in vivo*. Rejections regarding *in vivo* subject matter are moot in light of the present amendments, and Applicant, therefore, respectfully requests that the rejection under 35 U.S.C. §112, 1st paragraph (enablement) be withdrawn.

Response to §102(e) Rejections

Claims 1, 2, 5, 7-9, 11 and 22 remain rejected under 35 U.S.C. §102(e) as being anticipated by Fire *et al.* ("Fire;" USP 6,506,559). Applicant's claimed invention is presently drawn only to a method of disrupting targeted gene expression *in vitro* in a population of *human* cells by exposing the cell to a dsRNA homologous to the target gene thereby initiating RNA interference.

Applicant relies upon the attached detailed Declaration of Dr. Alan M. Gewirtz to explain why Fire fails to anticipate Applicant's present invention teaching the use of dsRNA in *human* cells. In accordance with the recent decision of *Phillips v. AWH Corp.*, No. 03-1269, -1286 (Fed. Cir., July 12, 2005), page 10, it is entirely proper for the inventor to speak as one of ordinary skill in the art about his invention.

> That starting point [for interpreting claim construction] is based on the well settled understanding that inventors are typically persons skilled in the field of the invention and that patents are addressed to and intended to be read by others of skill in the pertinent art. . . . Importantly, the person of ordinary skill in the art is deemed to read the claim term not only in the context of the particular claim in which the disputed term appears, but in the context of the entire patent, including the specification.

As further explained in the Declaration, Fire taught only the use of dsRNA in embryonic invertebrate cells in the '559 patent, but failed to recognize or address the intracellular defense problems anticipated in a mammalian cell that would have been expected, at the time of the Fire invention, to preclude use of dsRNA in such a mammalian cell to inhibit expression of a target gene *in vitro.* As a result, as demonstrated in Fire's own subsequent publications (previously provided to the Patent Office), and by the publications establishing the state of the art at least at the filing date of the Fire patent, and for several years thereafter (see, *e.g.*, Paddison *et al.*, *Proc. Nat'l Acad. Sci.* 99(3):1443-1448 (Feb. 5, 2002), attached hereto) neither Fire nor his peers believed that the method claimed in the '559 patent would be effective in a mammalian cell without substantial additional experimentation to overcome recognized problems. And even at that late date no one had any workable solution to permit the use of dsRNA in a viable, fully-responsive mammalian cell. Any suggestion by Fire was purely speculation that the claimed method demonstrated in an embryonic invertebrate cell

"hopefully" could be applied without substantial experimentation to overcome the intracellular defense mechanisms in a mammalian cell.

The art at the time of the Fire invention was well aware of the substantial problems expected in a mammalian cell, but at that time, no one – including Fire - knew how to introduce dsRNA into such a cell without initiating those defenses. Indeed, at the filing date of the application for the '559 patent, Fire was not in possession of such information.

Consequently in all fairness, the '559 claims cannot now be broadly read to include a methods for initiating RNAi in a mammalian cell, if Fire could not state definitively that gene-triggered silencing in vertebrates cells would result from the practice of his claimed invention. Fire understood, and the art at the time of his invention understood, what was not expressly stated in claim 1 of the '559 invention – that is, that the claimed invention was known to be operable, and it was believed to be operable, only in an invertebrate cell that did not contain intracellular defense mechanisms that would be activated against the introduction of foreign dsRNA.

Nevertheless, Applicant was not deterred from Fire's statements that his '559 patented method was unlikely to be effective in vertebrate cells. Contrary to the wisdom and expectations of other skilled practitioners in the art, Applicant set about inducing RNA interference in human cells by exposing several different cell lines of such cells to dsRNA homologous to a target gene. More importantly, Applicant showed – for the first time – that in a mammalian (human) cell population, RNA interference (RNAi) was actually induced in a target gene – *i.e.*, target gene expression was disrupted *in vitro* at the mRNA level in a human cell by small interfering RNA guide sequences that are homologous to a portion of the target gene. Accordingly, contrary to the Fire patent – Applicant's results in a mammalian (human) cell population is, indeed, definitive. Consequently, Applicant's seminal discovery was neither anticipated, nor obvious, in light of the art.

While the Fire patent may in fact be valid as to methods of treating cells of nematodes or invertebrate animals – the '559 methods are not enabling for mammalian cells – nor do they expressly claim a method that is effective in mammalian cells. As pointed out in his own later work, Fire did not believe that the '559 invention would be

effective in mammalian cells. Thus, if Fire, who certainly represents one of at least ordinary skill in the art did not believe in the ability to practice his own invention in vertebrates, the '559 patent is not enabling for use by others of ordinary skill in the art without undue experimentation, but with a reasonable expectation of success of the Fire method in vertebrate cells, or more specifically in human, cells – nor is such a use even suggested.

We are guided in this matter as previously stated in the record by *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 220 USPQ 303, 315 (Fed. Cir. 1983) which recognized that "patents are written to enable those skilled in the art to practice the invention, not the public." In this case however, one of ordinary skill, Fire, stated a year after his invention, that he did not believe that his invention could be practiced in mammalian cells. Moreover, *Gore* teaches that "A disclosure must be 112 compliance in light of knowledge extant in the art on itsexamined for application filing date. *Gore, supra* at 316. A method of Fire's invention was not known or tested by the patentee in mammalian cells at the time of his invention. A printed publication must also be enabling. *Constant v. Advanced Micro-Devices Inc.*, 7 USPQ2d 1059, 1063 (Fed. Cir. 1988). However, a specification which teaches how to make and use the invention in terms which correspond in scope to the claims can only be taken itself being an enabling reference if there is [no] "reason to doubt the objective truth of the statements relied upon therein for enabling support." *In re Marzocchi*, 169 USPQ 367, 369 (CCPA 1971); *Staehelin v. Secher*, 24 USPQ2d 1513, 1516 (BPAI 1992); *Fiers v. Sugano*, 25 USPQ2d 1601, 1607 (Fed. Cir. 1993).

A very recently decided case is quite helpful in understanding the enablement concept, although *In Re Kumar*, No. 04-1074, U.S. App. LEXIS 17215 (Fed. Cir., Aug. 15, 2005) is directed to §103 obviousness, rather than §102 anticipation, the concepts are identical. The *Kumar* court stated in its summary that:

> To render a later invention unpatentable for obviousness, the prior art must enable a person of ordinary skill in the field to make and use the later invention. *Beckman Instruments, Inc., 892 F.2d at 1551*; *Payne, 606 F.2d at 314*. Thus the relevant inquiry is not whether the Rostoker patent was invalid for lack of enablement, but whether Rostoker enabled persons skilled in this art to produce particles of the size and distribution claimed by Kumar. Of course, if it were shown that the Rostoker product could not be produced by the Rostoker method, that

would be relevant evidence concerning whether Rostoker rendered obvious the Kumar product.

While it is agreed that an enabling prior art reference need not be a blue print for Applicant's invention, in the case of the Fire '559 patent there was a recognized reason why one would not at the time of the invention have expected the Fire patented methods to operate successfully in mammalian cells. Yet Fire failed to identify the known problem, and offered no teaching what-so-ever for how to overcome it permitting the claimed methods to be effective for use in mammalian cells, and in his own later writings, Fire questioned whether the claimed invention could be effective in mammalian cells.

As clearly reiterated in the *Phillips* decision at page 11, the terms in the claim cannot be read in a vacuum, but rather in the context of the meaning to one of ordinary skill in the art at the time of the invention. See *Phillips* and decisions cited therein at page11. Therefore, although a patent reference is entitled to its broadest reading, it is not permissible to later read non-enabled meanings or operability into such claims that involve life forms to which the patent claims are silent, in a specification that fails to address known, anticipated problems to be overcome before the invention could be used in a mammalian cell. This is particularly true when the inventor himself *later* states that he does not believe the invention can function as claimed.

Applicant, therefore, requests the withdrawal of the rejection that relies upon Fire as teaching anything beyond treatment of invertebrate cells, and more specifically nematode cells. Fire fails to teach or enable a method to disrupt or inhibit expression of a target gene in a vertebrate cell *in vitro*, and therefore, is not prior art for such a purpose. The '559 patent does not, and cannot anticipate Applicant's claimed invention – which is specific to *human* cell.

Please note, that while Paddison *et al.*, *Proc. Nat'l Acad. Sci.* 99(3):1443-1448 (Feb. 5, 2002) is attached hereto to show the state of the art in 2002, it is not prior art to Applicant's actual filing date of November 14, 2001. Consequently,the Paddison refernce is not cited on a form 1449, nor is a fee accompanying this filing for the late addition of a prior art reference. If, however, such a citation or fee is required, the Examiner is requested to charge any such fee to Deposit Account 50-0573, as indicated at

the beginning of this Response; and Applicant's will, if asked, forward the citation on Applicant's Form 1449 as a supplemental reference.

Conclusion

Based on the foregoing, all pending claims are believed in condition for allowance. An early and favorable action toward that end is earnestly solicited.

Respectfully submitted,

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